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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,716	11/30/2000	David F. O'Brien	15907-0022	4843

25213 7590 02/14/2005

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT PAPER NUMBER

1615

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/728,716

Applicant(s)

O'BRIEN ET AL.

Examiner

Gollamudi S Kishore, Ph.D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 4-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 4-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment dated 9-28-04 is acknowledged.

Claims included in the prosecution are 1 and 4-39.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly added claim recites the limitation that polymerizable co lipid is not 1, 2 Bis----- phosphatidylcholine when the liposome forming lipid is dioleoylphosphatidylethanolamine or dioleoylphosphatidylcholine. A careful review of the specification as originally filed shows no support for this limitation and therefore, deemed to be new matter.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 4, 9-11, 16-17, 23, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992) of record.

Lamparski discloses liposomes containing a phospholipid (phosphatidylethanolamine or phosphatidylcholine) and a polymerizable co lipid (sorbPC) (note the abstract, Materials and Methods and Discussion).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the global transition temperature of the liposomes disclosed in Lamparski are substantially below the room temperature and that the temperature at which the liposomes disclosed in Lamparski would potentially form discrete domains would be at a temperature which is below the room temperature. Applicant in particular, based on the declaration by Dr. O'Brien argues that the main transition temperature of DOPC and DOPE (used by Lamparski) are -20 and -10 degrees respectively and that that the main phase transition temperature of the bis-sorb PC used is 27 degrees. According to applicant, at 3:1 molar ratio with bis-sorb PC, the global transition temperature would have been substantially below the room temperature. These arguments are deemed to be speculative since the reference of Bennett and O'Brien (Biochemistry, vol. 34, 1995) already of record indicates to be otherwise. In this publication, Bennett et al find that the global transition temperature of the same mixture (DOPE/bis-sorb PC) to be 49 degrees, which is well above the room

temperature (see Table 1 on page 3105). It is also interesting to note that applicant claims the same DOPE and DOPC in the newly added claim 39.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 4-5, 9-11, 16-31-33, 36 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above in view of either Heldebrant (5,061,484) or Charych (6,180,135) in further combination with Hallahan (6,159,443).

The teachings of Lamparski have been discussed above. In essence, Lamparski teaches instant liposomes and the destabilizing effect of ultra-violet on the liposomal membrane. What are lacking in Lamparski are the teachings of the use of X-rays for polymerization of the lipids and destabilizing the liposome. Although Lamparski does not specifically teach a method of administration of a therapeutic agent of a diagnostic agent, based on the studies Lamparski suggests the applicability of the radiation

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induced destabilizing of the liposome and the regulation of the release of the biological agents (note page 693).

Heldebrant while disclosing the administration of liposomal compositions to tumor bearing mice teaches that liposomal lipids can be polymerized by either UV radiation or by X-rays (col. 5, lines 14-23 and Example 4).

Charych teaches that liposomal lipids can be polymerized by either UV radiation or by X-rays (col. 11, lines 41-64).

It would have been therefore, obvious to one of ordinary skill in the art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use. Lamparski teaches only the application of ultraviolet radiation as the source as the ionizing radiation. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any form of ionization as long as they polymerize the lipid.

Hallahan discloses X-ray guided drug delivery to treat various neoplasms. The method involves administering the therapeutic agent or diagnostic agent in a delivery vehicle (liposomes) and irradiating the tissue using X-rays. The liposomes also contain antibodies attached to them. According to Hallahan such a method improves the drug delivery to the desired tissues (note the abstract, col. 1, line 61 through col. 6, line 58, col. 7, line 65 through col. 9, line 18, col. 15, line 18 through col. 17, line 9, col. 20, lines 6-49, col. 23, lines 10-59, Examples and claims).

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The use of X-rays as the ionizing radiation with the liposomes of Lamparski would have been obvious to one of ordinary skill in the art since X-rays are not only another form of ionizing radiation to polymerize the liposomal lipids as shown by Heldebrant or Charych, but also provide an improved method of delivery when combined with delivery vehicles such as liposomes as shown by Hallahan.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant while agreeing that Charych does teach that X-rays are another polymerization means, argue that Charych does not teach the administration of his liposomes to patients. The examiner points out that this reference was used to show that one could polymerize the lipids by X-rays; the reference of Lamparski is suggestive of such an administration.

Applicant argues that the purpose of polymerization in Heldebrant is different. This argument is not found to be persuasive since this reference was used to show that polymerization could be performed by X-rays. Similarly, applicant argues that Hallahan does not teach or suggest the administration of an ionizing radiation sensitive liposome to a patient. This argument is not found to be persuasive for the same reason. Furthermore, Hallahan teaches the concept of attaching antibodies to liposomes to deliver the drugs to the desired tissues.

7. Claims 5-8, 12-15, 34-35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above in view of either Heldebrant (5,061,484) or Charych (6,180,135) in further combination with Hallahan (6,159,443) as set forth above, further in view of Woodle (BB, 1992) of record.

The teachings of Lamparski, Heldebrant, Charych and Hallahan have been discussed above. What are lacking in Lamparski and other references are the teachings of the inclusion of PEG in the liposomal compositions.

Woodle discloses that the inclusion of hydrophilic polymers such as PEG in liposomes stabilizes the liposomes and also improves the circulation time of these sterically stabilized liposomes when administered (pages 180-185 and 194-195).

The inclusion of PEG in liposomes of Lamparski would have been obvious to one of ordinary skill in the art since such an inclusion stabilizes the liposomes and also improves their circulation time when administered.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Lamparski, Heldbrant, Charych and Hallahan have already been addressed above. Applicant argues that Woodle does not cure the deficiencies of the other references. This argument is not found to be persuasive since as recognized by applicant, Woodle teaches the use of pegylated lipids in lipids and the motivation to use these lipids in liposomes.

The reference of Singh 5,366,881 is cited of interest.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK